Electron-Induced Mass Spectrometry of 1,2-Dihydropyridine Derivatives

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The electron-induced mass spectrometry of 1-substituted-4-phenyl-1,2-dihydropyridines is characterized by a [*M*-1] peak that accounts for the base peak, and a fragment corresponding to the loss of the *N*-substituent in every example examined. (J Am Soc Mass Spectrom 1997, 8, 1255–1256) © 1997 American Society for Mass Spectrometry

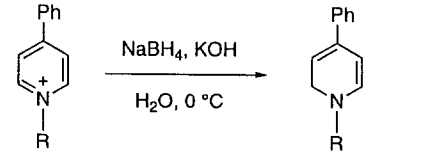
If the electron-induced mass spectrometry (EIMS) of 1,4-dihydropyridine derivatives has been well-documented [1, 2], the mass spectrometry of unsubstituted 1,2-dihydropyridines remained unreported, reflecting the difficult synthesis of this class of compounds and the few examples of these highly unstable derivatives [1]. In the course of our studies on the mechanism of action of neurotoxic 1,4-disubstituted-1,2,3,6-tetrahydropyridines [3–6], the authors were led to prepare some 1-substituted-4-phenyl-1,2-dihydropyridine derivatives. We report here the EIMS fragmentation of these type of compounds.

Material and Methods

Gas chromatography-electron ionization mass spectrometry (GC-EIMS) (70 eV) was performed on a Hewlett Packard 5890 GC fitted with an HP-1 capillary column which was coupled to a Hewlett Packard 5870 mass-selective detector. Data were acquired using an HP 5970 Chemstation. A scan range of 350–50 amu was employed to acquire the MS data, and 4 spectra were obtained for each compound. Calculations at the semiempirical level were performed by using AM1 [7] within MacSpartan software (MacSpartan Inc). Restricted Hartree–Fock approximation was used for closed-shell system and unrestricted Hartree–Fock was used for radicals. The dideuterated pyridinium **6-2,6-d_2** was prepared according to the literature, by treatment of the pyridinium **6** with NaOD in D_2O at 25 °C [8].

Results

Four 1-substituted-4-phenyl-1,2-dihydropyridine analogs were prepared by reduction of the corresponding pyridiniums (Scheme 1) [9, 10], and the EIMS (70 eV) of these compounds was recorded.



1 R = Phenyl
2 R = Cyclopropyl
3 R = Vinyl
4 R = CO_2Me

5 R = Phenyl
6 R = Cyclopropyl
7 R = Vinyl
8 R = CO_2Me

Scheme 1. Preparation of 1-substituted-4-phenyl-1,2-dihydropyridine derivatives **5–8**.

All spectra were characterized by the loss of one amu and the [M-1] ion accounted for the base peak in every case (Figure 1, Table 1). In analogy with the fragmentation of 1,4-dihydropyridine derivatives [2, 11], the [M-1] ions presumably account for the corresponding pyridinium ions and the mechanism leading to this [M-1] fragment is likely to be a loss of hydrogen atom from the C2 position. In support to this hypothesis, the 2-d_1-*N*-vinyl **7-2-d_1** analog was prepared and a mixture of [M-1] and [M-2] ions was detected on the mass spectrum. The isotope effect associated with the loss of hydrogen/deuterium from the C2 position was estimated to be 1.7. Loss of the *N*-substituent was also observed in all cases, leading to a m/z = 156 ion, and in correlation with this fragment, ions corresponding to the *N*-substituent were also detected in every example (m/z = 77 for **5**; m/z = 41 for **6**; m/z = 27 for **7**; m/z = 59 for **8**).

Interestingly, in the case of the cyclopropyl deriva-

Table 1. Relative abundance (%) of $[M]^{\cdot +}$, $[M-1]^+$, and [156] ions

	N Substituent	$[M]^{\cdot +}$	$[M-1]^+$	[156]
5	Phenyl	34	100	17
6	Cyclopropyl	52	100	38
7	Vinyl	54	100	20
8	CO_2Me	45	100	42

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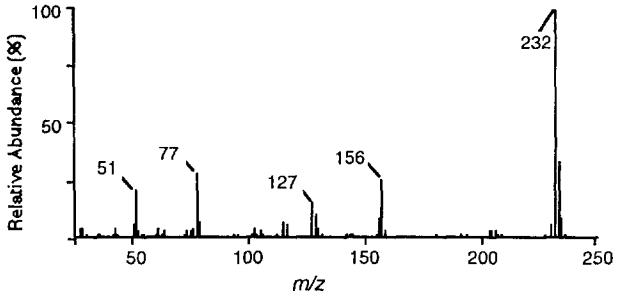
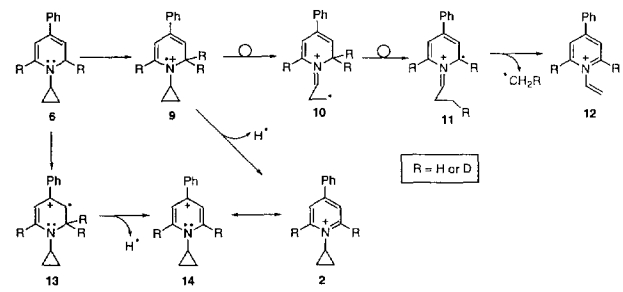


Figure 1. EIMS (70 eV) of 1,4-diphenyl-1,2-dihydropyridine (**5**).

tive **6**, a [M-15] ion **12** was also observed (53%). In 1,2,3,6-tetrahydropyridine derivatives, a similar fragmentation was shown to originate from a cyclopropyl ring opening and 1,5-hydrogen shift from the C6 position followed by loss of a methyl group [12]. The [M-1] ion was then very small (<10% relative to the [M-15]), which was expected on the basis of the very fast cyclopropyl ring opening of cyclopropyl aminyl radical cations ($>10^{-11}$ s^{-1}) [13–15]. Similarly, in order to observe the formation of pyridinium **2**, the loss of hydrogen atom would have to compete with the extremely fast cyclopropyl ring opening. Although the α-C–H bond energy is 5.1 kcal/mol (AM1) weaker in the case of the dihydropyridine **6**, which should favor the partitioning between ring opening and hydrogen loss toward the hydrogen loss, a mixed ionization on the nitrogen, **9**, and the conjugated double bonds system, **13**, could also account for both fragmentation processes (Scheme 2). In support to this hypothesis is the representation of the highest occupied molecular orbital (HOMO) energy (AM1 level) showing the availability of the electrons of the π-conjugated system (Figure 2).

In order to support the mechanism of 1,5-hydrogen shift and the loss of methyl group, the dideuterated pyridinium **1-2,6-d_2** was prepared and reduced with $NaBD_4$ to yield the trideuterated dihydropyridine **6-2,2,6-d_3** (m/z = 200). The EI mass spectrum revealed a peak at m/z = 184, corresponding to the loss of 16 amu



Scheme 2. Proposed fragmentation pathways leading to the pyridinium ions $[M-1]^+$ (**2**) and $[M-15]^+$ (**12**).

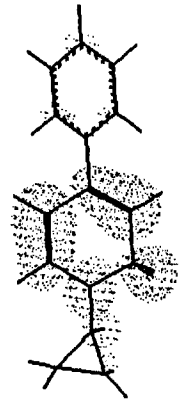


Figure 2. Representation of the HOMO energy of 1-cyclopropyl-4-phenyl-1,2-dihydropyridine (**6**).

and consistent with a 1,5-deuterium shift from the C2 position to the terminal methylene of the *N*-substituent (Scheme 2) followed by loss of CH_2D to give the vinyl pyridinium ion **12-2,6-d_2**. The presence of a [M-2] ion as the base peak also confirms the loss of deuterium from the C2 position to the likely pyridinium ion **2-2,6-d_2**.

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